

Clinical Importance of Late Recurrence in Soft-Tissue Sarcomas

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Background and Objectives: Soft-tissue sarcomas (STS) represent a diverse histologic group of malignancies at risk for local and distant failure. We studied the impact of late (5 or more years) vs. early recurrence (less than 5 years) on subsequent outcome.

Methods: Four hundred sixty-eight patients with STS treated between 1962 and 1992 were evaluated for late ($n = 39$; 8%) or early ($n = 253$; 54%) recurrence. Clinical and pathologic factors were reviewed. Survival data were analyzed by the Kaplan-Meier method and the log-rank test.

Results: Of the 39 patients with a late recurrence (median follow-up 156 months), 18 patients had local recurrence, 7 patients developed distant recurrence, and 14 patients had local and distant recurrence. Thirty patients with late local and/or distant recurrence underwent complete or wide excision ($n = 16$), amputation ($n = 4$), or local resection ($n = 10$). The overall 5-year survival rate following late recurrence was 61%. The 5-year overall survival rate was statistically better for patients with a late local recurrence alone than for patients with distant failure, 94% vs. 36%, respectively ($P = 0.003$). Neither the site of the primary STS, age, primary margin status, nor histology had any effect on subsequent local or distant failure and subsequent survival.

Conclusions: These data suggest that an aggressive approach is appropriate in patients who present with late recurrence (more than 5 years) following treatment of the primary STS. Impressive survival rates can be achieved in the treatment of local recurrences.

J. Surg. Oncol. 2000;73:81–86. © 2000 Wiley-Liss, Inc.

KEY WORDS: distant metastases; local recurrence; sarcoma; survival

INTRODUCTION

Soft-tissue sarcomas (STS) arise, almost exclusively, from mesodermal structures [1]. In 1999, an estimated 7,800 cases of STS will occur in the United States and 4,400 patients will succumb to their disease [2]. These uncommon tumors are difficult to treat due to the diversity of the anatomic sites of involvement, grade, histology, and metastatic potential. Following treatment of the initial primary sarcoma, 40–60% of patients will have recurrence [3]. The majority of these recurrences are di-

agnosed within 2 years of primary STS treatment. However, late recurrences beyond 5 years can occur [4,5]. Factors that correlate with local and distant recurrence include tumor size, tumor grade, surgical margin, deep location, recurrent disease, and certain histopathologic

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Accepted 3 November 1999

subtypes [6,7]. Among these prognostic factors, high tumor grade is the most important predictor of disease-specific survival.

The natural history of late recurrence after management of the primary STS is unclear. We hypothesized that a late recurrence following treatment of the STS may represent a different biologic entity than an early recurrence by virtue of the factors leading to the later presentation. We evaluated the outcome of patients who developed a late recurrence compared to patients who had an early recurrence following treatment of the primary STS.

MATERIALS AND METHODS

The medical records of patients treated at the Roswell Park Cancer Institute (RPCI) for recurrent STS were retrospectively reviewed. Local recurrence was defined as disease within or adjacent to the previous surgical dissection bed in patients with STS following treatment of the primary lesion. Late recurrence was defined as occurring at 5 or more years and early recurrence less than 5 years following treatment of the primary STS. Four hundred seventy-seven patients from the sarcoma/melanoma and bone database with a minimum of 5 years of follow-up from June 1962 to June 1992 were evaluated to identify those who developed local or distant recurrence. All patients underwent surgical resection with the operative goal of achieving negative surgical margins. For tumors of the extremities, limb preservation was attempted.

The following clinicopathologic variables were evaluated: age, sex, site of the primary STS, grade, size, TNM stage [8], histopathologic subtype, primary operation, surgical margins, site and timing of failure, treatment of recurrence, and subsequent status. The patients were followed every 3 months for the first 3 years, then every 6 months until 5 years posttreatment, and annually thereafter.

Statistical Analysis

The distribution of patient, tumor, and treatment characteristics between the late and early recurrence groups was evaluated by the Cox test [9]. Overall survival rate rather than the disease-specific survival rate was selected as an endpoint to avoid the possibility of excluding patients dying of apparent unrelated causes who might have had undocumented recurrent disease as the cause of their death. Differences in the overall survival rate in patients with late and early recurrence were calculated by the method of Kaplan and Meier [10] and comparison made using the log-rank test. The Cox proportional hazards model was used for the multivariate analysis.

RESULTS

All Patients

The medical records of 477 patients were reviewed. Records were unavailable or incomplete for 9 patients

TABLE I. Tumor Characteristics of the Primary STS*

Characteristic	No.
Site	
Extremity	166
Trunk	53
Retroperitoneum	63
Head and neck	10
Grade	
Low	31
Intermediate	65
High	157
Unknown	38
Size (cm)	
<5	32
≥5	187
Unknown	73
Stage	
I	14
II	47
III	125
IV	22
Unknown	84
Histopathologic subtype	
Liposarcoma	76
MFH	62
Leiomyosarcoma	35
Synovial	22
Hemangiopericytoma	13
Fibrosarcoma	15
MPNST	5
Other	64
Surgical margin	
Positive	25
Negative	148
Unknown	119
Postoperative chemotherapy	
Yes	89
No	198
Unknown	5
Postoperative radiotherapy	
Yes	97
No	187
Unknown	8

*MFH, Malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor.

and were not included in the analysis. Thus, the records for 468 patients were evaluated. Recurrence occurred in 292 patients after a median follow-up of 70 months (1–451 months). The clinical and pathologic features of late and early recurrence of STS are shown in Table I. The study population was composed of 167 men and 125 women with a mean age of 46 years (range 18–91 years). The distribution of local and distant recurrences for the extremity (166 of 279), trunk (53 of 84), retroperitoneum (63 of 83), and head and neck (10 of 22) were 59%, 63%, 76%, and 45%, respectively. Two hundred twenty-two patients had intermediate or high-grade primary STS, whereas 31 had low-grade histology. Of these 31 patients, 5 (16%) manifested a higher histologic grade at recurrence than the original low-grade tumor and suc-

TABLE II. Distribution of Early and Late Recurrences Following Treatment of the Primary STS

Type	No. (%)	
	Early	Late
Local recurrence alone	72 (28)	18 (46)
Local and distant	74 (29)	14 (36)
Distant recurrence alone	107 (43)	7 (18)

cumbed to their disease after multiple recurrences. The survival rate from primary treatment for the whole group was 65% at 5 years, 50% at 10 yrs, and 40% at 15 years.

Early Recurrence

Two hundred fifty-three patients (54%) with a median follow-up of 45 months (3–451 months) were found to have their first recurrence within 5 years following treatment of the primary STS. Patients who had early recurrence had a larger tumor size (11 vs. 9 cm; $P = 0.02$), higher grade (56% vs. 36%; $P = 0.01$), and higher stage ($P = 0.02$) compared to the patients with late recurrence. Postoperative chemotherapy after primary resection was given to a significantly higher number of patients in the early recurrence group (33% vs. 15%; $P = 0.03$).

The majority of early recurrences consisted of distant failure ($n = 182$). Seventy-two patients presented with local recurrence alone and 74 patients presented with local and distant recurrence (Table II). Of the 146 patients with early local with or without distant recurrence, 141 patients underwent surgical resection, whereas surgical resection of distant metastases was attempted in 113 of the 181 patients. Seventy-two patients received systemic chemotherapy and 21 patients postoperative radiotherapy. The remaining nonsurgical candidates were offered systemic chemotherapy. In patients with early recurrence, 60 patients (24%) were alive without evidence of disease, 17 patients (7%) were alive with disease, 165 patients (65%) died of disease, and 11 patients (4%) died of other causes.

Late Recurrence

Thirty-nine patients (8%) developed a late recurrence at a median follow-up of 156 months (range 73–398 months) after treatment of the primary STS. Local recurrence alone was most common in patients with late recurrence (Table II). Of the 32 patients with late local recurrence, 30 patients underwent further surgery directed at the local recurrence site including complete or wide excision ($n = 16$), amputation ($n = 4$), or local resection ($n = 10$). Thirteen patients received additional postoperative radiotherapy. In contrast, 15 of the 21 patients with distant recurrence underwent attempted metastectomy or a combination of systemic chemotherapy

and radiotherapy. Six patients with distant metastases were treated with systemic chemotherapy only.

The median follow-up after the first recurrence for the late recurrence group was 104 mos. (range 60–188 months) compared with 18 mos. (range 1–60 months) for the early recurrence group. Following treatment of the late recurrence, 19 patients (49%) were alive without evidence of disease, 5 patients (13%) were alive with disease, 14 patients (36%) died of disease, and 1 patient (2%) died of other causes. There was a statistically significant difference in survival rate at 10 years (84% vs. 31%) and 15 years (57% vs. 25%) between the groups with late and early recurrence from the initial primary STS treatment ($P < 0.0001$).

The overall 5-year survival rate following late recurrence was 61%. The overall 5-year survival rate for patients who presented with late local recurrence alone was significantly better than those who presented with local and distant disease or distant disease alone, 94% vs. 36% and 33% ($P = 0.001$), respectively. When the groups were compared for survival rate after first recurrence, there was no statistically significant difference in survival between the groups with late and early local recurrence (5-year 94% vs. 81%, $P = 0.42$; Fig. 1).

There was a prolongation in median survival time in patients with late vs. early distant recurrence from 18.7 to 42.3 months. However, this did not reach statistical significance in 5-year survival following first recurrence (34% vs. 19%; $P = 0.08$).

When the late and early recurrence groups were evaluated by multivariate analysis, early recurrence, distant with or without local recurrence, larger tumor size, and performance of the procedure at RPCI were unfavorable prognostic factors for survival after first recurrence (Table III). For local recurrence alone, smaller tumor size was the only favorable prognostic factor for survival after first recurrence (Table IV).

Recurrence: RPCI Vs. Outside Institution

A significant difference was noted in the number of patients ($n = 165$) who were referred from other institutions for management of recurrence, either late or early (85% vs. 52%; $P = 0.0001$). Of 165 patients, 33 with late recurrence and 132 patients with early recurrence were referred from outside institutions. As might be suspected, patients who were referred from outside institutions had a significant proportion of incomplete information concerning their primary STS including grade, size, stage, and status of the surgical margin. Of the 273 patients treated for the primary STS at RPCI, 6 (2%) and 121 patients (44%) developed a late and early recurrence, respectively. Patients treated at RPCI had a statistically significant difference in the number of patients with larger and higher-grade primary STS. The RPCI-treated group was found to have a greater proportion of early

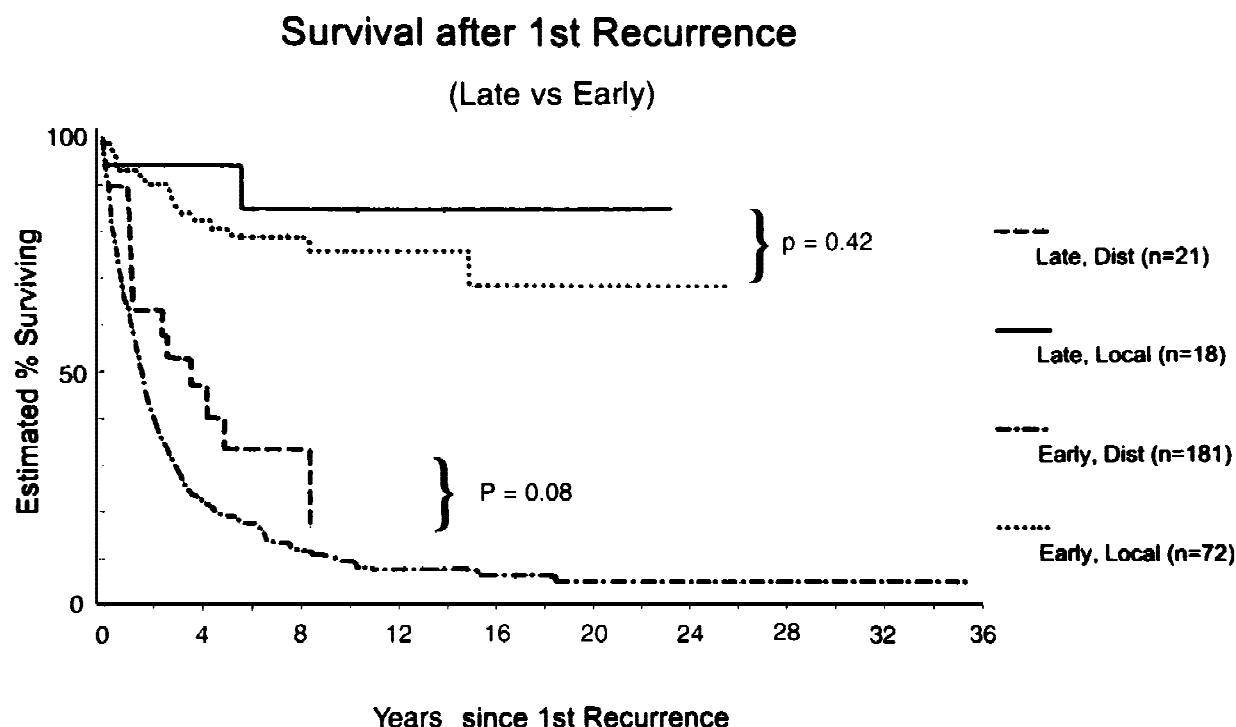


Fig. 1. Survival after first recurrence for local and distant, late vs. early recurrence. There is no significant difference in survival for patients who present with local recurrence either late or early ($P = 0.42$). Although there appears to be an early survival benefit for patients presenting with late distant recurrence, this was not statistically significant.

TABLE III. Multivariate Analysis of Survival After First Recurrence for Late and Early Recurrences

Variable	β -coefficient	P
Recurrence		
Late vs. early	1.6	0.001 ^a
Type of recurrence	0.47	0.0001 ^b
Tumor characteristic		
Site of primary	0.02	0.44
Grade	-0.08	0.85
Size	0.04	0.0004 ^c
Stage	0.64	0.23
Treatment characteristics		
Procedure performed	-0.09	0.39
Surgical margin	-0.11	0.49
Postoperative chemotherapy	-0.09	0.65
Postoperative radiotherapy	-0.14	0.48

^aEarly recurrence worse.

^bDistant and/or distant and local worse.

^cLarger tumor size worse.

distant recurrence (102 vs. 79, $P < 0.0001$) and consequently poorer 5-year survival after first recurrence compared to patients referred from the outside (12% vs. 28%, $P = 0.01$).

DISCUSSION

Despite improvement in the multidisciplinary management of STS, local and distant failure following treatment of the primary sarcoma continues to occur [11,12].

TABLE IV. Multivariate Analysis of Survival After First Recurrence for Local Recurrence Alone

Variable	β -coefficient	P
Recurrence		
Late vs. early	1.2	0.41
Tumor characteristic		
Site of primary	0.22	0.10
Size	0.11	0.02 ^a
Grade	7.1	0.95
Stage	-5.1	0.96
Treatment characteristics		
Procedure performed	-0.66	0.13
Surgical margin	-1.1	0.08
Postoperative chemotherapy	0.19	0.89
Postoperative radiotherapy	-2.0	0.06

^aSmaller tumor size better.

In order to properly manage these patients, a thorough understanding of the biology of STS recurrences, as well as the timing and type of recurrence, is required. Biologic factors that may be operative in late vs. early recurrent tumors include tumor, host, and treatment interactions [13]. Noteworthy, 16% (5 of 31) of patients with initial low-grade tumors manifested a higher histology than the original tumor and succumbed to their disease. This biologic phenomenon could not be analyzed further due to the small sample size. In this study, early recurrences were associated with more aggressive tumor characteristics including grade, size, and stage. These features may

be related to the higher incidence of distant metastases within 5 years of treatment of the primary STS and worse outcome following first recurrence by multivariate analysis. In contrast, favorable tumor characteristics such as low tumor grade and early stage may have led to the slower regrowth of residual tumor in patients presenting with late recurrence.

Approximately 50% of late recurrences in this study were local failure alone, whereas 75% of early recurrences were distant with or without local recurrences. Distinguishing between local recurrence alone vs. local recurrence with synchronous distant micrometastases is difficult. The controversy between the association of local recurrence with subsequent survival has continued since the classic work of Cantin et al. [14]. Of 653 patients with STS of the trunk and extremities treated at Memorial Cancer Center from 1935 to 1959, 187 patients (29%) had recurrence. The deleterious influence on survival was attributed to three facts. First, patients presenting with local recurrence had a higher frequency of synchronous distant metastases than did those presenting for management of the initial primary STS (22% vs. 11%). Second, patients with local recurrence had a higher mortality rate from sarcoma than those without recurrence (61% vs. 30%). Third, distant metastasis was more common in patients with one or more local recurrences than in those without recurrence (65% vs. 24%). An earlier report from our institution examining local recurrence as a time-dependent covariable showed a 2.5 times higher risk of dying after recurrence [15]. Thus, the previously reported inferior outcome of patients found to have a local recurrence may be due to synchronously undetected distant metastases [16–21]. However, an aggressive multidisciplinary approach (surgical resection and radiotherapy) and improvement in metastatic workup, excluding synchronous distant disease following the detection of a late local recurrence, in this series resulted in a subsequent 85% 10-year survival rate.

Patients who present with a late or early distant failure with or without local recurrence pose a difficult clinical problem. A selected number of patients with late and early distant recurrence may benefit from metastatectomy [22–24]. In this study, patients who were found to have late distant recurrence were treated with an aggressive approach including surgical resection as an integral component resulting in a prolongation of survival from 18.7 to 42.3 months compared to patients with early distant recurrence. Although the improvement in survival was not statistically significant ($P = 0.08$), it is possible that larger patient numbers and a longer follow-up interval in the late distant recurrence group might have been required to further clarify the difference. Treatment strategies for this group of patients should continue to be individualized in a multidisciplinary manner. The selective usage of positron emission tomography scanning

may be effective in identifying patients with multiple sites of metastatic disease who should receive systemic treatment [25].

The timing, pattern, and efficacy of treatment of early or late recurrence are critical factors in determining the subsequent management of these patients following treatment of the primary STS. Our data indicate that patients found to have late recurrence, especially local recurrence alone, have improved survival with an aggressive multidisciplinary approach. However, a better understanding of the biology of STS resulting in late and early recurrence is required to maximize our effort in this disease process.

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